Antiviral resistance among influenza A viruses and interim guidance for use of antivirals

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CDC

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Overview

- Review of influenza testing and treatment
- Current status of antiviral resistance in United States
- Interim guidelines for antiviral use
- Looking ahead and summary

Human Influenza

- Highly transmissible respiratory illness caused by influenza viruses
- Yearly winter epidemics (seasonal or interpandemic influenza)
- Sporadic, unpredictable pandemics
- Three strains in circulation among humans
  - Influenza A subtypes (H1N1) and (H3N2)
  - Influenza B

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Influenza A: Antigenic Drift and Shift

- Antigenic drift - Continual process
  - Point mutation or recombination in viral genes
  - Diminished immune response among previously infected or immunized persons to “drifted” strains
  - Results in yearly epidemics
  - Requires that vaccine updated yearly
  - Can cause changes in susceptibility to antivirals

- Antigenic shift - Sporadic, unpredictable event
    - Replacement of HA or HA + NA (i.e., new subtype) from an animal influenza A
    - No immunity within the population
    - Can result in a pandemic

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Annual Interpandemic Influenza Impact

- 2.5-20% of population ill
  - Highest rates in children
  - Attack rates over 30% in children reported
- Average of >36,000 deaths (wide range)
  - >90% in those >64 years
- Average of >200,000 hospitalizations (wide range)
  - About 50% in those >64 years
  - Risk of hospitalization for children <2 years similar to elderly
- Substantial economic impact
  - Burden of annual epidemics estimated at $87.1 billion annually

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Influenza Clinical Diagnosis

Clinical symptoms are non-specific

- Symptoms overlap with many pathogens (“influenza-like illness”)
- Laboratory data needed to verify diagnosis
- Even at peak influenza season, about 25-35% of specimens from persons with symptoms of acute respiratory infection test positive for influenza

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Laboratory Testing for Influenza Virus*

- Viral culture
  - Gold standard but results take 7+ days usually
  - Source of influenza isolates for yearly vaccine development
- Serology
  - Must use paired serum samples
  - >2 week delay for results
- Immunofluorescence
  - Requires intact cells and laboratory skill/experience
- Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)
  - Most sensitive
  - Becoming more widely available
  - Some state health and reference labs can distinguish influenza A subtype
- Rapid antigen tests
  - In most studies, 70+% sensitive, 90+% specific in children but likely (much) lower for adults
  - Can provide results <30 minutes and be done in clinic

*Specific information on tests: http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm

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Rapid Influenza Diagnostic Tests*

Advantages

- Provide results ≤ 30 minutes (NP or nasal swab)
- Useful for detecting outbreaks
- Useful for clinical management
- Simple procedures, variety of settings
- Some can distinguish influenza A from B

Disadvantages

- Less accurate than viral culture
  - Sensitivities 50-75%; Specificities 90-99%
  - PPV highest during peak influenza activity
- Limited information obtained
- **None able to identify influenza A subtype**

*Specific information on tests: http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm

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Predictive Values of Screening Tests* and Prevalence of Influenza Viruses

- High influenza prevalence (peak influenza activity)
  - PPV Highest
  - NPV Lowest (false negatives)
- Low influenza prevalence (sporadic activity)
  - PPV Lowest (false positives)
  - NPV Highest
- **gold standard = viral culture*

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Influenza Testing during Periods of High Activity within the Community

- During peak season, some clinicians order less testing
  - Rely on clinical diagnosis
  - Provide empiric treatment to some severely ill patients with acute febrile respiratory illness, or patients at higher risk for complications of influenza
  - Rationale: Predictive value of a negative test is low during peak season is low – so concerned about false negatives
    - Only about 25-35% of ARI will be influenza even during peak season

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Persons for whom antiviral treatment should be considered*

If possible, antiviral treatment should be started within 48 hours of influenza illness onset. The effectiveness of initiating antiviral treatment >48 hours after illness onset has not been established.

Persons for whom antiviral treatment should be considered include:

- persons hospitalized with laboratory-confirmed influenza;
- persons with laboratory-confirmed influenza pneumonia;
- persons with laboratory-confirmed influenza and bacterial coinfection;
- persons with laboratory-confirmed influenza infection who are at higher risk for influenza complications; and
- persons presenting to medical care with laboratory-confirmed influenza within 48 hours of influenza illness onset who want to decrease the duration or severity of their symptoms and transmission of influenza to others at higher risk for complications.

*Source: ACIP Recommendations for Prevention and Control of Influenza, 2008
http://www.cdc.gov/flu/professionals/acip/index.htm

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Persons for whom antiviral chemoprophylaxis should be considered during periods of increased influenza activity in the community*

- Persons at higher risk for complications during the 2 weeks after influenza vaccination if influenza viruses are circulating in the community;
- Persons at higher risk for whom influenza vaccine is contraindicated;
- Family members or health-care providers who are unvaccinated and are likely to have ongoing, close exposure to persons at higher risk;
- Persons at higher risk, and their family members and close contacts, when circulating strains of influenza virus in the community are not matched with vaccine strains;
- Persons with immune deficiencies or those who might not respond to vaccination; and
- Unvaccinated staff and persons during response to an outbreak in a closed institutional setting with residents at high risk (e.g., extended-care facilities).

*Source: ACIP Recommendations for Prevention and Control of Influenza, 2008
http://www.cdc.gov/flu/professionals/acip/index.htm

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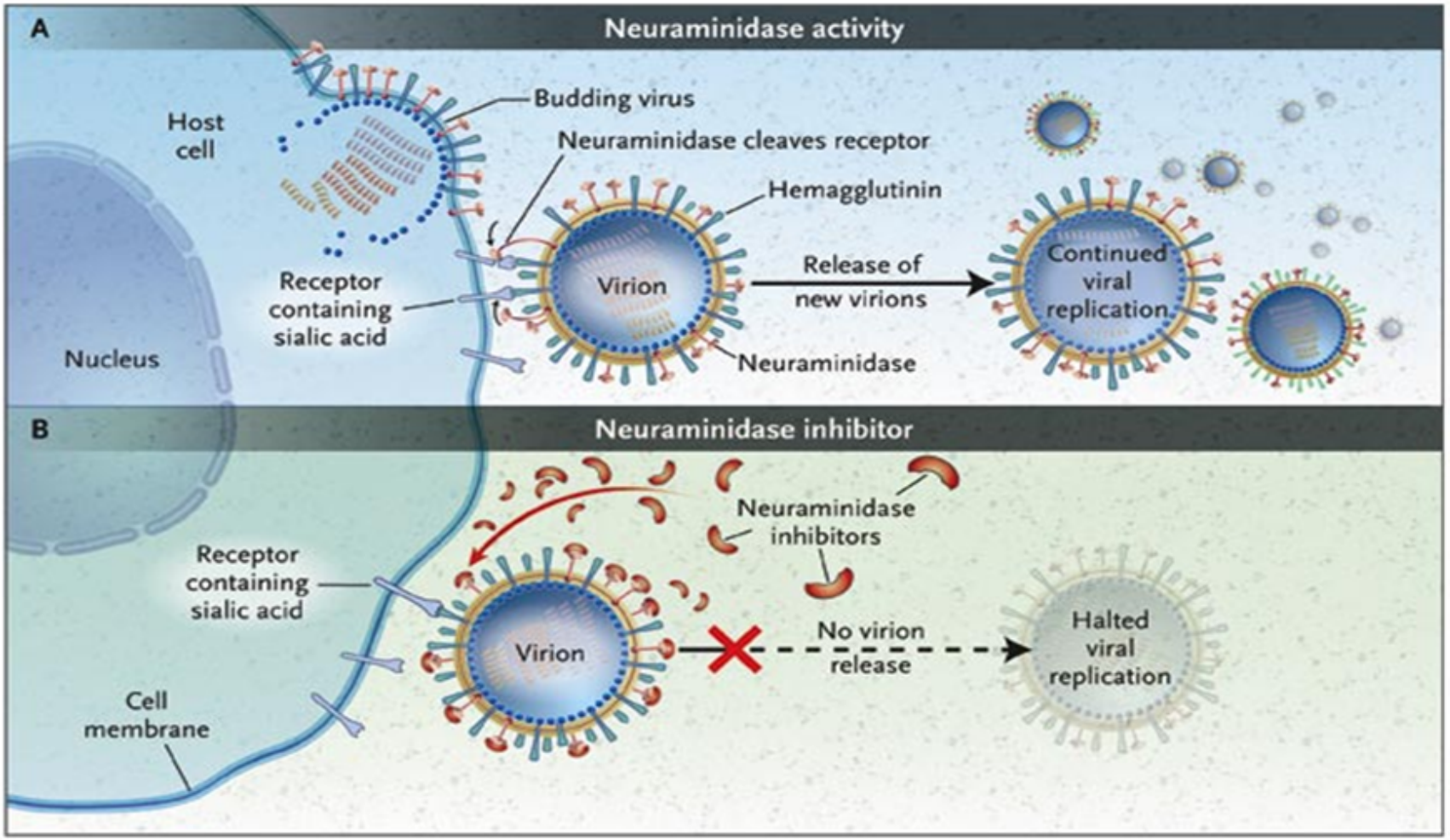
Antivirals for Treatment or Prevention of Influenza

Neuraminidase Inhibitors

- Oseltamivir (Tamiflu - Roche) and Zanamivir (Relenza - GSK)
  - Used for the treatment and prevention of seasonal influenza A and B virus infections
  - Treatment should begin as soon as possible after symptom onset, and benefits only proven if started within 48 hours of onset



Source: Moscona, A. (2005). Neuraminidase Inhibitors for Influenza. N Engl J Med 353: 1363-1373

Neuraminidase Inhibitors

- Effectiveness in treating seasonal influenza:
  - Reduces duration of influenza symptoms by average of 1-1.5 days when administered within 2 days of illness onset based on randomized placebo-controlled clinical trials (RCT)
    - Recent observational study showed benefit even when treatment started >48 hours after onset*
  - Reduces lower respiratory tract complications, pneumonia, and hospitalization in some observational studies
    - Recent observational study indicated oseltamivir reduces mortality among hospitalized patients with lab-confirmed seasonal influenza A virus infections*

*McGeer et al. Clin Infect Dis 2007

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Neuraminidase Inhibitors

- Effectiveness in preventing seasonal influenza (chemoprophylaxis):
  - Prevents influenza infection among exposed household members in RCT (70-90% effectiveness) when started within 48 hours of exposure
  - Prevents infection when given daily to persons at risk for influenza complications during influenza season (70-90% effectiveness), e.g., nursing home setting

Oseltamivir

- Available as a capsule or suspension administered by mouth
- Approved in the U.S. for treatment or prevention of influenza in persons aged ≥1 year
  - Treatment for 5 days
  - Prevention regimen typically continues for 10 days after exposure
- Pediatric dosage depends on age and weight
- For treatment of seasonal influenza, administered twice a day for 5 days
- Side effects: nausea, vomiting in some persons
- Reports of delirium in pediatric patients (adolescents, most reports from Japan)
  - Warning added to label in 2007

Oseltamivir (2)

- Precautions
  - People with kidney disease (reduce dose)
  - Pregnant or nursing women (safety unknown)
- Resistance
  - Can develop with treatment, although clinical importance unknown
  - Resistance uncommon until 2007-08 season

Zanamivir

- Orally inhaled powder – administered by mouth via special device
- Approved in the U.S. for
  - treatment of seasonal influenza (aged ≥7 years)
  - prevention of seasonal influenza (aged ≥5 years)
- Treatment dosage: two puffs in the morning and two at night for 5 days (5 days)
- Prevention dosage: 2 puffs once a day (typically for 10 days after exposure)
- Side effects
  - Wheezing, and breathing problems
  - Concerns that reports of delirium associated with oseltamivir might indicate drug class effect
    - Warning added to label in 2008

Zanamivir (2)

- Precautions
  - People with chronic respiratory disease
  - Pregnant or nursing women (safety unknown)
- Resistance
  - Can develop with treatment, although clinical importance unknown
  - Very low levels of resistance among influenza A (H1 and H3) viruses circulating

ACIP Recommendations 2008: Antiviral Dosage by Age

TABLE 4. Recommended daily dosage of influenza antiviral medications for treatment and chemoprophylaxis — United States

Antiviral agent	Age group (yrs) 1–6	7–9	10–12	13–64	≥65
Zanamivir*					
Treatment, influenza A and	NA	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
	1–4	**5–9**			
Chemoprophylaxis, influenza A and	NA	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir					
Treatment† influenza A and B	Dose varies by child's weight§	Dose varies by child's weight§	Dose varies by child's weight§	75 mg twice daily	75 mg twice daily
Chemoprophylaxis, influenza A and B	Dose varies by child's weight¶	Dose varies by child's weight¶	Dose varies by child's weight¶	75 mg/day	75 mg/day

Source: ACIP Recommendations for Prevention and Control of Influenza, 2008
http://www.cdc.gov/flu/professionals/acip/index.htm

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Other Antivirals Active Against Influenza A Viruses: Amantadine and Rimantadine

- Chemically related, orally administered drugs referred to as adamantanes
- Reduce replication of influenza A viruses by inhibiting function of M2 ion channel
- No activity against influenza B
- Resistance develops rapidly with influenza A viruses
- High prevalence of resistance among human influenza A(H3N2) viruses
- Adverse effects include gastrointestinal and neurological symptoms
- **Not currently recommended for use as a single agent for treatment**

No additional antiviral agents expected to be available in near future

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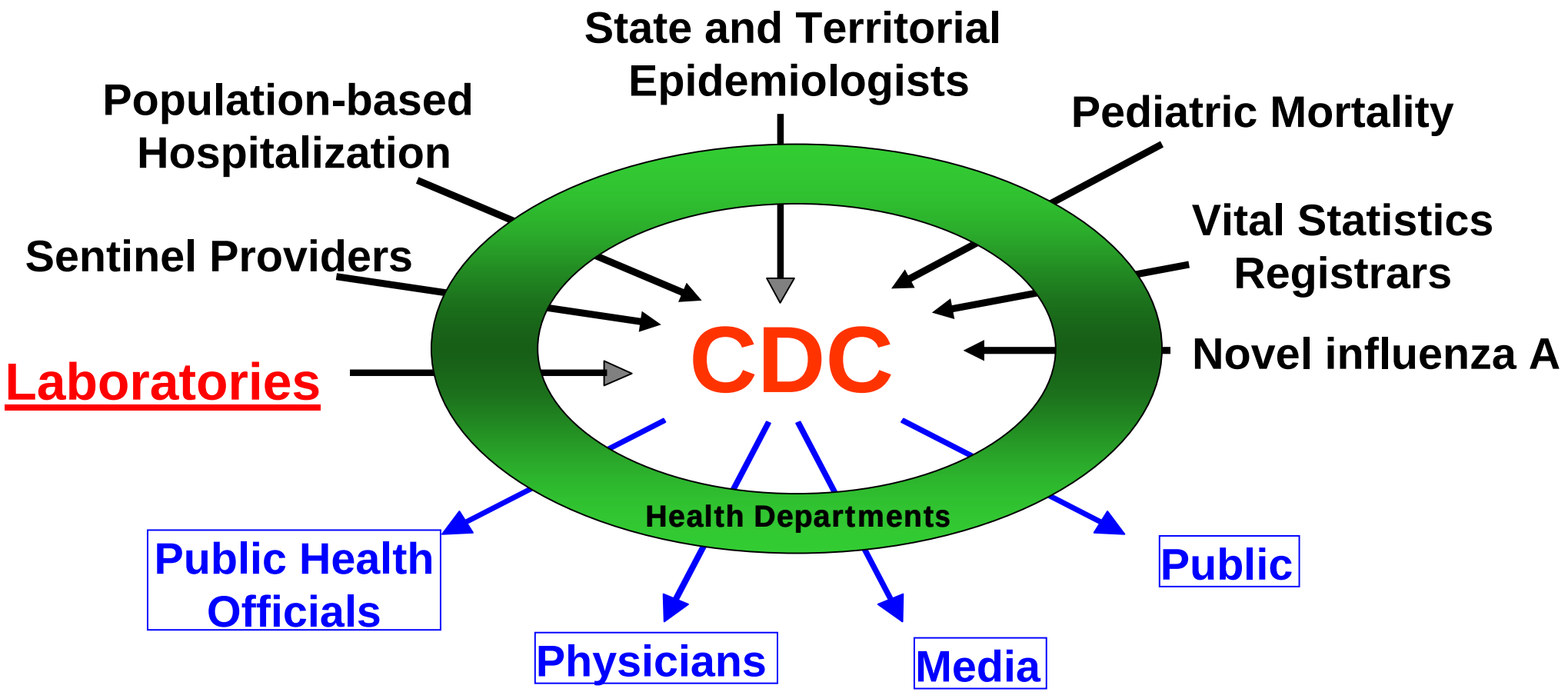
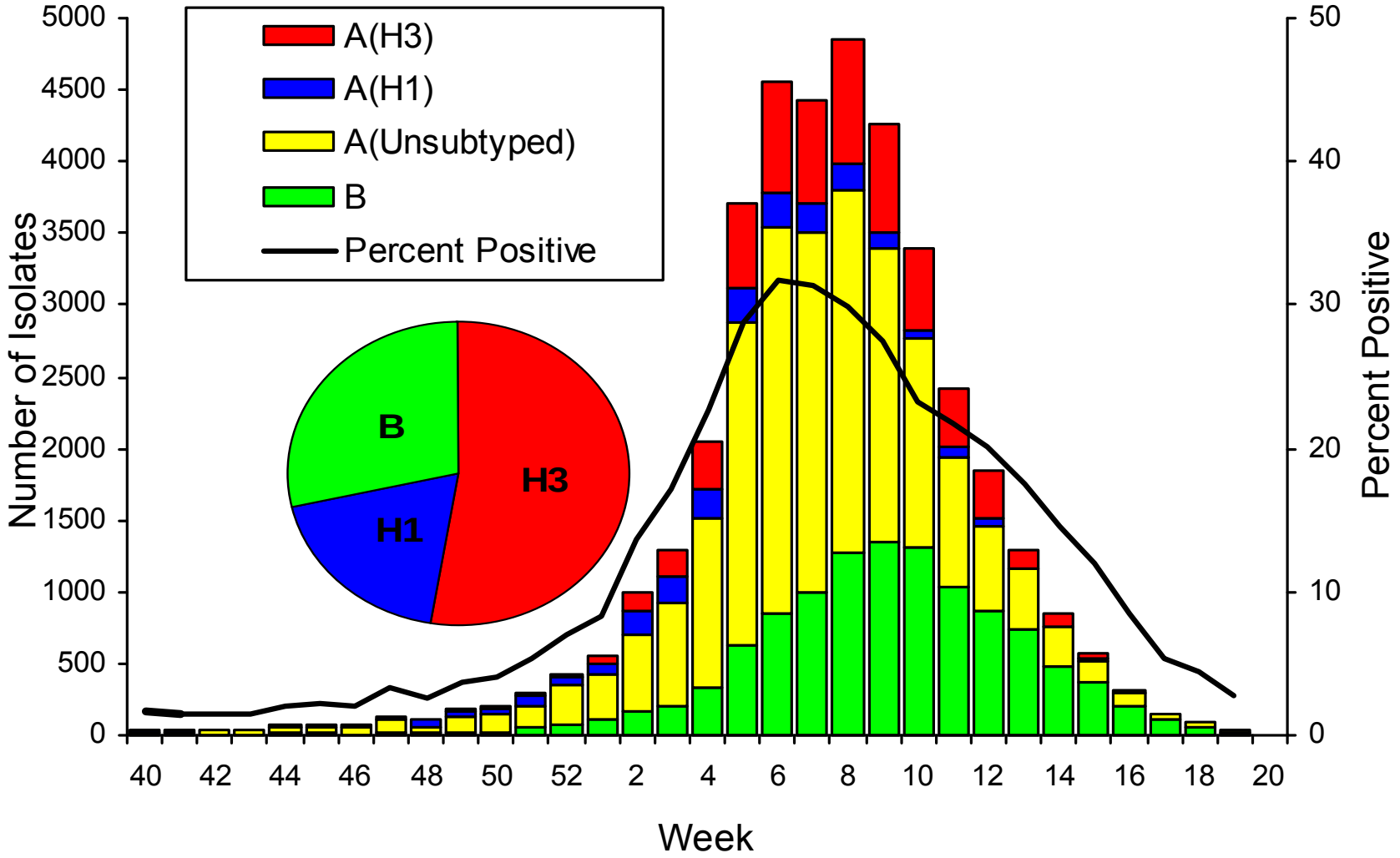
National Influenza Surveillance System



U.S. WHO/NREVSS Collaborating Laboratories National Summary, 2007-08



229,329 samples tested; 39,827 positive for influenza

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Emergence of Oseltamivir Resistance among Influenza A(H1N1) Viruses: 2007-2008 Influenza Season

- United States, end of season*
  - 123 (11.9%) of 1,026 influenza A (H1N1)
    - 4 (0.7%) of 588 in 2006-07
  - Adjusting for subtype prevalence, an estimated 2.1% of all influenza A and B viruses in circulation in the United States were resistant to oseltamivir
- Worldwide, end of Northern hemisphere season**
  - 1,203 (16%) of 7,535 influenza A(H1N1) viruses tested were resistant to oseltamivir
  - All oseltamivir-resistant A (H1N1) viruses had same genetic mutation (H274Y) in the neuraminidase gene

Clinical Characteristics of Influenza Caused by Oseltamivir-Resistant Influenza A(H1N1)

- U.S., 2007-08 season*
  - Among 99 patients with influenza caused by oseltamivir-resistant influenza A (H1N1)
    - None took oseltamivir prior to testing
    - None had household contacts taking oseltamivir prior to their onset of illness
  - When compared to oseltamivir-sensitive influenza A (H1N1) illnesses, similar
    - Clinical illness
    - Severity of illness
    - Risk groups affected
- EU, 2007-08 season
  - Oseltamivir use not the cause of increases in resistance
  - Clinical characteristics same as for infection with oseltamivir-sensitive viruses

* N Dharan, et al CDC unpublished data

**ECDC 28 Aug 2008. http://ecdc.europa.eu/en/Health_topics/influenza/antivirals.aspx

CDC

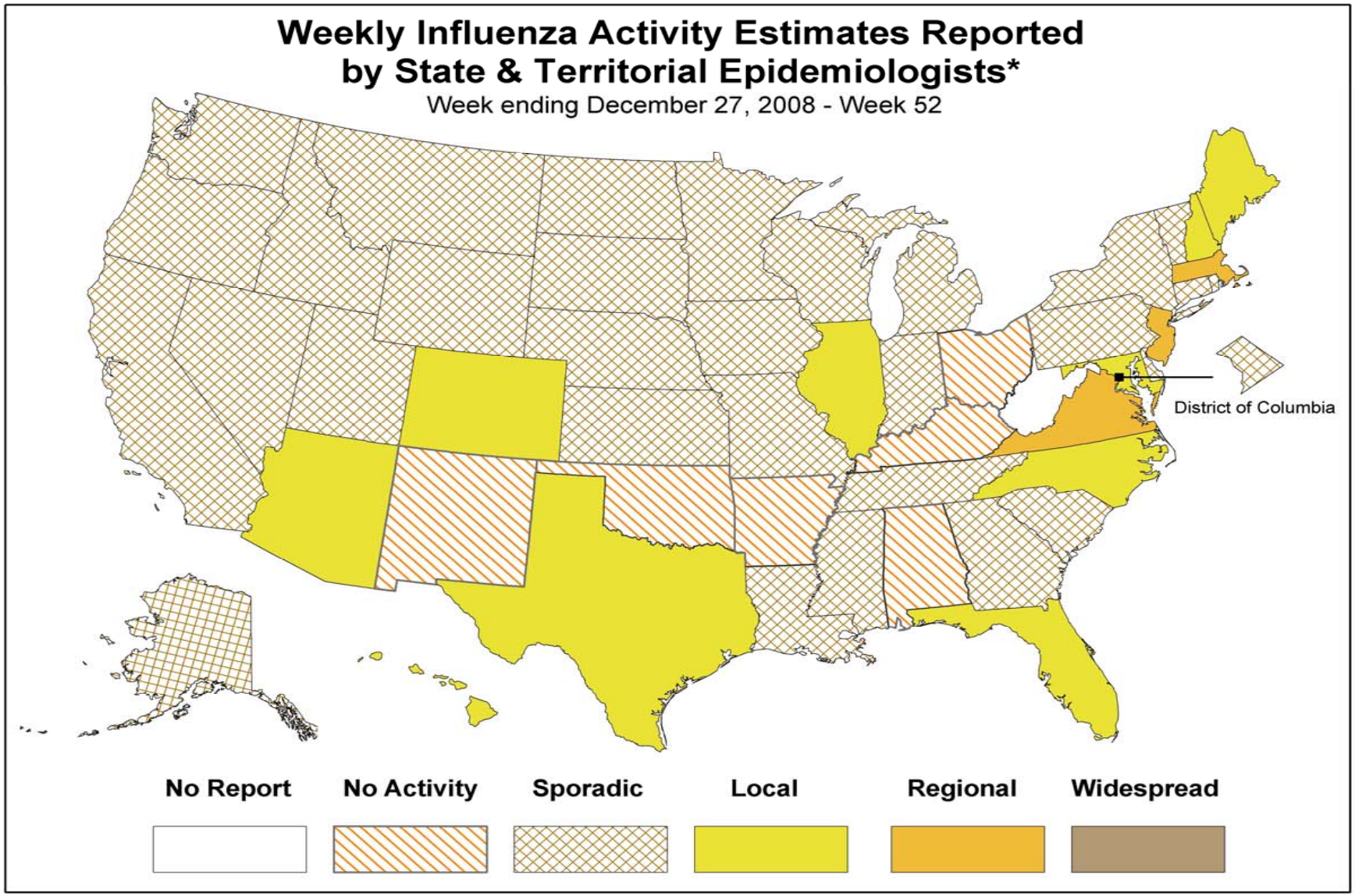
Current status of antiviral resistance in United States

Antiviral Resistance

Situation Update

- At this point in the season, a low level of influenza activity has been reported in the United States. As a result, few viruses have been available for antiviral resistance testing.
- Since October 1, 2008, the following viruses from 21 states have been tested for antiviral resistance:
  - 73 influenza A (H1N1) viruses
  - 11 influenza A (H3N2) viruses
  - 33 influenza B viruses
- 58% of the influenza A viruses tested were from only 3 states

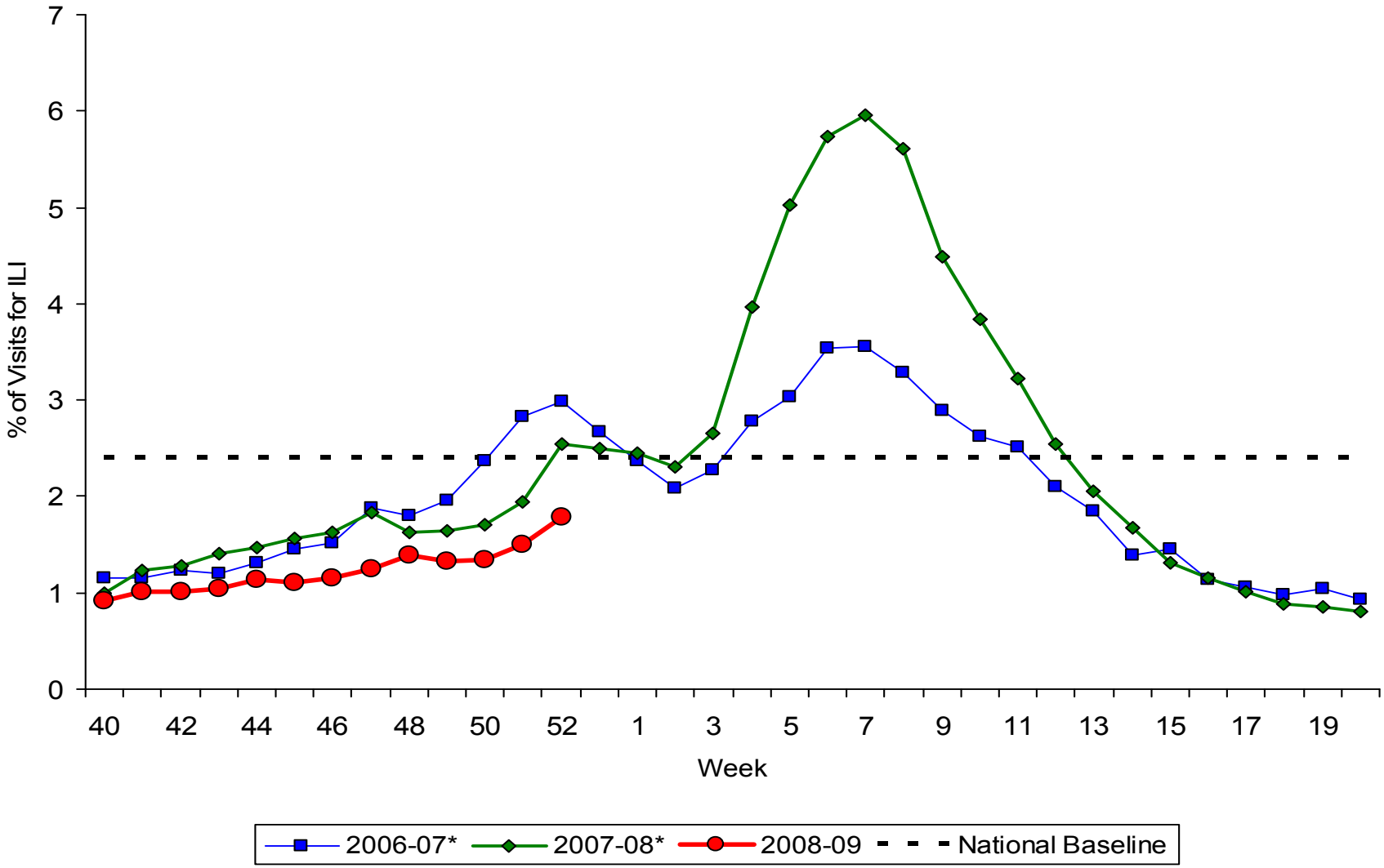
CDC



* This map indicates geographic spread & does not measure the severity of influenza activity

Weekly FluView available at: http://www.cdc.gov/flu/weekly/fluactivity.htm

Percentage of Visits for Influenza-like Illness (ILI) Reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet), National Summary 2008-09 and Previous Two Seasons



Weekly FluView available at: http://www.cdc.gov/flu/weekly/fluactivity.htm

Antiviral Resistance 2008

Neuraminidase inhibitor resistance:

- 72 of 73 influenza A (H1N1) viruses tested were resistant to oseltamivir.
- All 73 influenza A (H1N1) viruses were sensitive to zanamivir.
- All 11 influenza A (H3N2) viruses were sensitive to oseltamivir and zanamivir.
- All influenza B viruses tested were sensitive to oseltamivir and zanamivir.

CDC

Antiviral Resistance 2008 (Continued)

Adamantane Resistance
(Amantadine and Rimantadine)

- 73 influenza A (H1N1) and 11 influenza A (H3N2) viruses were tested for adamantane resistance.
  - All influenza A (H1N1) viruses were sensitive to amantadine and rimantadine.
  - All influenza A (H3N2) viruses tested were resistant to the adamantanes.
  - The adamantanes (amantadine and rimantadine) are not effective against influenza B viruses.

CDC

Summary of antiviral resistance 2008-2009

	Influenza Strains		
Antiviral	**H1N1**	**H3N2**	**B**
Adamantanes*	Susceptible	≈ 100%	≈ 100%
Oseltamivir**	~ 100%	Susceptible	Susceptible
Zanamivir	Susceptible	Susceptible	Susceptible

* Data from several seasons

** Data from a small number of isolates, 2008-2009 season

CDC

Oseltamivir resistance: Summary

- Resistance probably developed as part of antigenic drift process
- No evidence that increasing resistance is driven by oseltamivir use
  - Japan: 75% of global oseltamavir use but low prevalence of resistance
  - Norway: first country with reports of resistance, but oseltamivir rarely used
- No evidence that oseltamivir-resistant viruses are different for oseltamivir-sensitive viruses with regard to:
  - Transmissibility
  - Virulence (severity of illness and types of complications)
  - Prevention with vaccination

CDC

Clinical Management Issues – Implications of resistance among influenza A(H1N1) viruses

- No test for antiviral resistance available to clinicians for decision-making
- Rapid tests that can distinguish influenza A from B available
- No rapid test to distinguish H3N2 from H1N1 (subtyping)
  - State health laboratories and some reference labs can subtype
- Empiric (no diagnostic test) treatment often used when influenza activity high
- Many clinicians don't use or rarely use antivirals
  - 54% of primary care physicians reported any use in 2007 survey
  - <50% of hospitalized patients are treated

CDC

CDC activities in response to increased oseltamivir resistance among A (H1N1) viruses

- Prior to season
  - Developed enhanced viral surveillance in partnership with state public health labs
  - Increased throughput and timeliness of antiviral testing in CDC labs
  - Response scenarios discussed with consultants and ACIP workgroup

- During season to date
  - MMWR with season update in December 2008
  - FluView updated weekly including antiviral resistance data
  - Discussed with GSK, Roche
  - Developed draft Health Alert Network (HAN) advisory with interim guidelines

Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season*

*Adapted from Health Alert Network Advisory issued December 19, 2008.

Available at http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279

Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season

- Early season data indicates that oseltamivir-resistant H1N1 is the most commonly isolated virus thus far
  - Strain predominance typically changes as seson progresses
- Clinicians need to know that oseltamivir alone might not effectively prevent or treat influenza
- Health Alert Network advisory issued December 19, 2008

CDC

Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Key Points

- Treatment with zanamivir or a combination of oseltamivir and rimantadine is preferable in some situations

- Local influenza surveillance data and laboratory testing can help with physician decision-making regarding the choice of antiviral agents for their patients

- Oseltamivir-resistant H1N1 strains are antigenically similar or identical to the strains in the vaccine

CDC

Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Deciding which antiviral regimen to use

- Use influenza virus testing to help decision-making
  - A rapid test able to distinguish influenza A from influenza B is most useful
  - Patients who test positive for influenza B can receive oseltamivir or zanamivir – no preference
    - No oseltamivir resistance seen among B viruses

CDC

Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Deciding which antiviral regimen to use

- Review local or state influenza virus surveillance data weekly during influenza season, to determine which types (A or B) and subtypes of influenza A virus (H3N2 or H1N1) are currently circulating in the area
  - State health laboratories have the capacity to subtype influenza viruses
  - For some communities, surveillance data might not be available or timely enough to provide information useful to clinicians

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Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Scenarios

Rapid antigen or other laboratory test	**Predominant virus(es) in community**	**Preferred medication(s)**	**Alternative (combination antiviral treatment)**
1. Not done, or 2. Negative, but clinical suspicion for influenza	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
1. Not done, or 2. Negative, but clinical suspicion for influenza	H3N2 or B	Oseltamivir or Zanamivir	None

*Amantadine can be substituted for rimantadine but has increased risk of adverse events. Human data are lacking to support the benefits of combination antiviral treatment of influenza; however, these interim recommendations are intended to assist clinicians treating patients who might be infected with oseltamivir-resistant influenza A (H1N1) virus.

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Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Scenarios

Rapid antigen or other laboratory test	**Predominant virus(es) in community**	**Preferred medication(s)**	**Alternative (combination antiviral treatment)**
Positive A	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Positive A	H3N2 or B	Oseltamivir or Zanamivir	None

*Amantadine can be substituted for rimantadine but has increased risk of adverse events. Human data are lacking to support the benefits of combination antiviral treatment of influenza; however, these interim recommendations are intended to assist clinicians treating patients who might be infected with oseltamivir-resistant influenza A (H1N1) virus.

CDC

Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Scenarios

Rapid antigen or other laboratory test	**Predominant virus(es) in community**	**Preferred medication(s)**	**Alternative (combination antiviral treatment)**
Positive A/B	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Positive A/B	H3N2 or B	Oseltamivir or Zanamivir	None
Positive B	Any	Oseltamivir or Zanamivir	None

*Amantadine can be substituted for rimantadine but has increased risk of adverse events. Human data are lacking to support the benefits of combination antiviral treatment of influenza; however, these interim recommendations are intended to assist clinicians treating patients who might be infected with oseltamivir-resistant influenza A (H1N1) virus.

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Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season: Chemoprophylaxis Issues

- Persons who are candidates for chemoprophylaxis (e.g., residents in an assisted living facility during an influenza outbreak, or persons who are at higher risk for influenza-related complications and have had recent household or other close contact with a person with laboratory confirmed influenza) should be provided with medications most likely to be effective against the influenza virus that is the cause of the outbreak, if known.
-
- Respiratory specimens from ill persons during institutional outbreaks should be obtained and sent for testing to determine the type and subtype of influenza A viruses associated with the outbreak and to guide antiviral therapy decisions.

- Persons whose need for chemoprophylaxis is due to potential exposure to a person with laboratory-confirmed influenza A (H3N2) or influenza B should receive oseltamivir or zanamivir (no preference).

- Zanamivir should be used when persons require chemoprophylaxis due to exposure to influenza A (H1N1) virus.
  - Rimantadine can be used if zanamivir use is contraindicated.

- Oseltamivir + rimantadine might be needed in some outbreak situations. To reduce need for combination prophylaxis, seek out testing to help:
  - Subtyping to determine if influenza H3N2 or H1N1
  - If H1N1, antiviral resistance testing

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Challenges Associated with Zanamivir Use

- Method of administration: Zanamivir (an inhaled medication) not suitable for most severely ill patients
  - Age limitation
  - Contraindicated for patients with pulmonary disease
  - Difficult to administer to hospitalized patient with influenza
- Familiarity with use: Clinicians might not be familiar with zanamivir
- Availability: Limited in past seasons
  - GSK (pharmaceutical manufacturer) has increased supply available for 2008-09 season

CDC

Summary and Looking Ahead

CDC activities in response to increased oseltamivir resistance among A (H1N1) viruses

- During season to date
  - Enhanced viral surveillance implemented (improved representativeness)
  - MMWR December 2008
  - FluView updated weekly including antiviral resistance data
  - Discussed with GSK, Roche
  - Draft Health Alert Network (HAN) advisory with interim guidelines
  - Communications strategy and web update

- Expected
  - FluView will updated weekly including antiviral resistance data
  - MMWR in Feb 2009; Apr 2009
  - Potential for additional guidelines based on emerging surveillance data
  - ACIP vote on Influenza Prevention and Control (includes antiviral recommendations) Feb 2009
  - Monitor for severe infections or unusual outbreaks involving oseltamivir-resistant viruses

Strain Characterization, 2008-9 Season (FluView December 27,2008)*

CDC has characterized 104 viruses*

- A (H1) [n=68]:
  - 100% - A/Brisbane/59/2007-like viruses (similar to vaccine strain)
- A (H3) [n=7]
  - 100% - A/Brisbane/10/2007-like viruses (similar to vaccine strain)
- B [n=27]
  - 33% in B/Yamagata lineage (similar to vaccine strain)

Weekly FluView available at: http://www.cdc.gov/flu/weekly/fluactivity.htm

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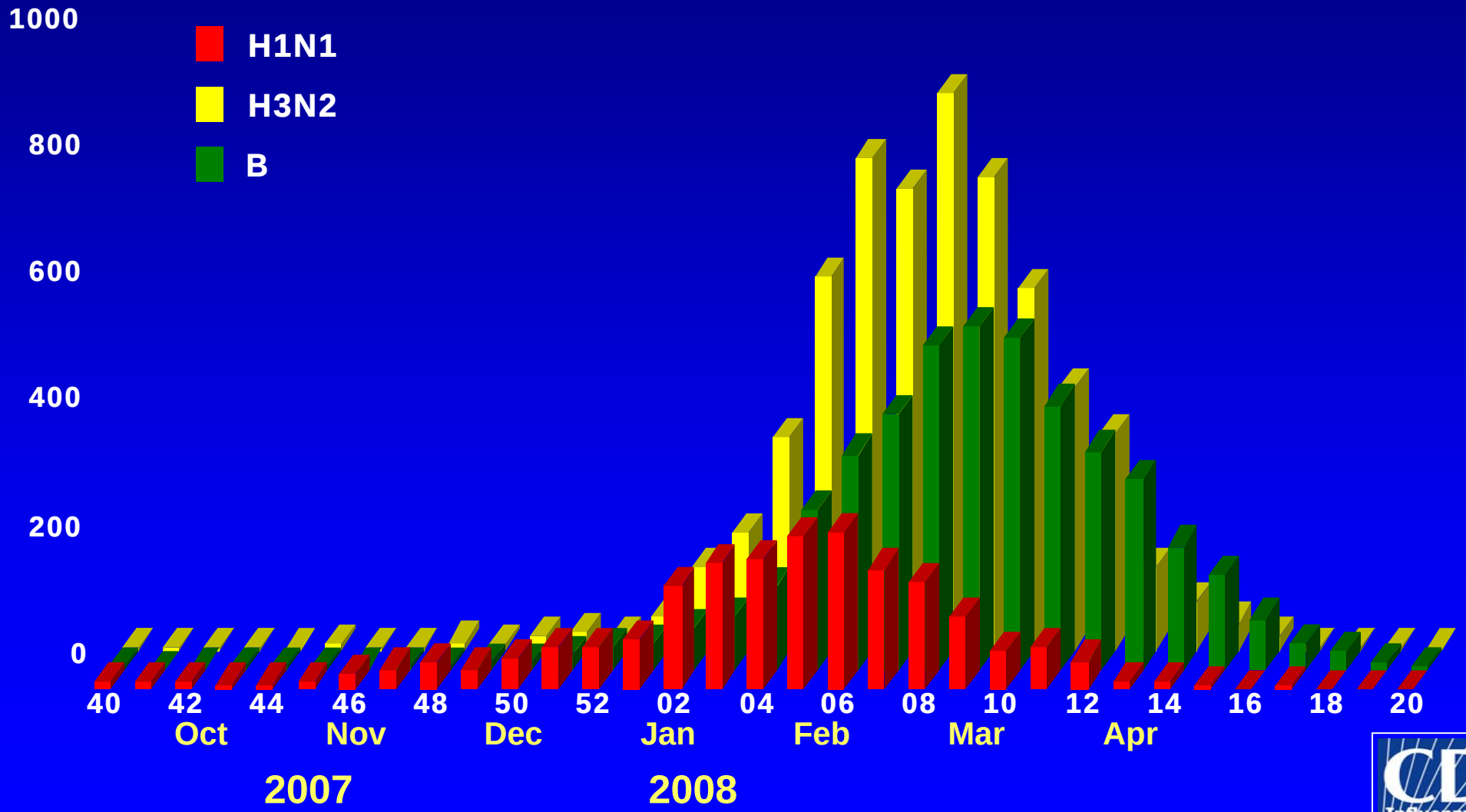
Summary: Meeting the Challenges Posed by Oseltamivir-Resistant Influenza A(H1N1) Viruses

- CDC is actively testing viruses to monitor antiviral resistance throughout the season
- Influenza viruses that are resistant to oseltamivir are sensitive to zanamivir and adamantanes (rimantadine and amantadine)
- Influenza viruses that are resistant to oseltamivir do not appear to be more dangerous or infectious

Summary: Meeting the Challenges Posed by Oseltamivir-Resistant Influenza A(H1N1) Viruses

- Use local virus surveillance data, clinical judgment, and rapid antigen testing to guide choice of antiviral regimen
- Clinicians should be alert to additional changes in antiviral recommendations - monitor CDC and state health department information sources
- Vaccination prevents influenza regardless of antiviral resistance – get vaccinated

Influenza Strains by type/subtype over time, USA, 2007-08



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